ACS Chemical Neuroscience Spotlight on CEP-1347

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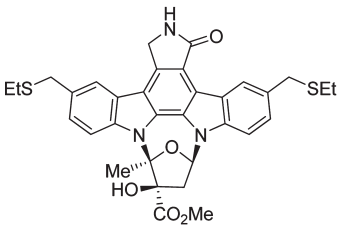
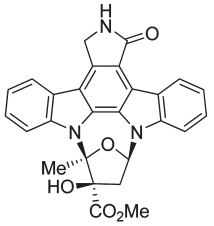


CEP-1347 (**1**)



(+) K-252a (**2**)

Parkinson's disease is the second most common chronic neurodegenerative disease, and is primarily characterized by the rigidity, akinesia, and tremor that results from the loss of dopaminergic neurons in the substania nigra. Existing therapies increase the levels of dopamine signaling in the brain and improve motor symptoms, but ultimately lose their effect because they do not inhibit the neuronal degeneration that underlies disease progression. A significant unmet medical need remains for therapies able to halt or delay the progression of motor dysfunction.

CEP-1347 (**1**) is an indolocarbazole kinase inhibitor originally discovered by Kyowa Hakko Kogyo in the course of a program investigating the neurotrophic properties of derivatives of the natural product K-252a (**2**). The c-Jun n-terminal kinases (JNKs) have been shown to play a key role in apoptosis of multiple neuronal populations including those of the substania nigra (*1*), and CEP-1347 blocks the activation of JNKs through ATP competitive inhibition of the upstream mixed lineage kinase (MLK) family (*2*). Although MLK3 is often mentioned as a primary target, CEP-1347 acts as a relatively broad-spectrum kinase inhibitor, and it remains unclear which MLK needs to be inhibited in neurons or whether multiple MLKs must be inhibited simultaneously in order to provide neuroprotection.

CEP-1347 exhibited pronounced neurotrophic and neuroprotective properties in vitro and in animal models of neurodegeneration (*3*, *4*). In particular, this inhibitor was able to reduce the loss of tyrosine hydroxylase immunoreactivity and dopamine transporter density in mice and monkeys following administration of the neurotoxin 1-methyl-4-phenyl-tetrahydropyridine (MPTP) (*4*, *5*). Additional mouse studies demonstrated that JNK pathway activation by MPTP is inhibited by CEP-1347. These findings supported the clinical investigation of CEP-1347 as a disease-modifying therapeutic in Parkinson's disease. Initial placebo-controlled dose-finding and tolerability studies revealed that CEP-1347 was well tolerated in young and elderly healthy volunteers up to doses of 50 mg twice daily (BID). The observation that CEP-1347 did not significantly affect striatal uptake of 2-β-carbomethoxy-3-beta-(4-iodophenyl)-tropane (β-CIT), a positron emission tomography (PET) imaging agent for assessing presynaptic dopamine transporter (DAT) activity, suggested that DAT activity measurements might be used as a secondary end point in efficacy trials (*6*).

The PRECEPT trial was a large (n = 806) trial designed to measure the ability of CEP-1347 to delay the time required for patients diagnosed with Parkinson's disease to begin dopaminergic therapy (*7*). Changes in the Unified Parkinson's Disease Rating Scale (UPDRS) and in dopamine transporter function as assessed by single photon emission computed tomography (SPECT) imaging of dopamine transporters were also assessed. The trial commenced enrollment in April 2002 and was halted in May 2005. At this point, 200 of the subjects had been observed for 24 months, and the average patient had been enrolled in the trial for over 21 months. In the placebo arm, 57% of the patients reached the primary clinical end point of requiring dopaminergic therapy. A similar proportion of the patients receiving CEP-1347 also reached this end point (10 mg BID 65%; 25 mg BID 59%; 50 mg BID 64%). UPDRS assessment indicated that there was a greater worsening among subjects in the CEP-1347 arms that was potentially dose dependent. Similarly, the β-CIT SPECT scans suggested that there was a significantly greater decline in striatal β-CIT (and presumably striatal dopamine transporters) in the CEP-1347 arms.

Unfortunately, the direct effect of CEP-1347 administration on inhibition of the MLK/JNK pathway in the CNS of human subjects could not be determined in the PRECEPT trial. Therefore, the failure of the PRECEPT trial has limited utility for assessing the relationship between JNK activity and neurodegeneration.

Received Date: August 23, 2010
Accepted Date: August 25, 2010
Published on Web Date: September 03, 2010

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DOI: 10.1021/cn1000793 | *ACS Chem. Neurosci.* (2011), *2*, 3–4

The fact that important questions regarding the utility of JNK pathway inhibition remain following a large and expensive clinical trial underscores the need for biomarkers that will allow assessment of biological activity and target inhibition in clinical trials. Similarly, it is unclear whether the clinical failure of CEP-1347 is indicative of limitations of the in vitro assays used to discover CEP-1347 or of the induced neuronal toxicity animal models of Parkinson's disease that supported its progression into clinical trials (*8*).

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DOI: 10.1021/cn1000793 | *ACS Chem. Neurosci.* (2011), *2*, 3–4